Regular Review

Diagnosis and management of diabetic autonomic neuropathy

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As the clinical importance of diabetic autonomic neuropathy has become recognised the need has grown for simple objective tests to confirm its presence or absence. This article is intended to give a practical guide to those tests which we consider reliable, reproducible, simple, and non-invasive. These criteria have so far been fulfilled only in tests based on cardiovascular reflexes. They also need to reflect damage elsewhere in the autonomic nervous system, and currently available evidence suggests that this is so.[1 2] Though tests using cardiovascular reflexes are most often done on diabetics, they are equally applicable in the diagnosis of autonomic damage caused by other disorders.

The tests described in table I are based on the responses of the heart rate and blood pressure to a variety of stimuli. The first three reflect cardiac parasympathetic integrity, while the other two start to give abnormal results with more severe sympathetic nerve damage. While each test may be used individually we think that all five should be performed when possible, so giving fuller information about the state of the autonomic nervous system.

Tests reflecting cardiac parasympathetic damage

Heart-rate response to Valsalva manoeuvre

During the strain period of the Valsalva manoeuvre the blood pressure drops and the heart rate rises. After release the blood pressure rises, overshooting its resting value, and the heart slows. Though these reflex changes are complex, the response of the heart rate can be abolished by atropine but it is unaffected by propranolol, suggesting that it is mediated by the vagus nerve.[3] In patients with autonomic damage the blood pressure slowly falls during strain and slowly returns to normal after release, with no overshoot rise in blood pressure and no change in heart rate.

The test is performed by the patient blowing into a mouthpiece connected to an aneroid manometer or a modified sphygmomanometer and holding it at a pressure of 40 mm Hg for 15 seconds while a continuous electrocardiogram is recorded. The manoeuvre is performed three times with one-minute intervals between. The test should be avoided in patients with proliferative retinopathy, because of the risk of retinal haemorrhage. Problems may also occur with patients with poor vision who are unable to see the manometer. Patients can cheat by sticking the tongue over the mouthpiece, but this is usually obvious to the observer.

The result is expressed as the Valsalva ratio,[4] which is the ratio of the longest R-R interval after the manoeuvre (reflecting the overshoot bradycardia following release) to the shortest R-R interval during the manoeuvre (reflecting the tachycardia during strain), measured with a ruler from the electrocardiogram trace. The mean of the three Valsalva ratios is taken as the final value. Interpretation of this and the other test results is shown in table II.

Heart-rate (R-R interval) variation during deep breathing

Normally the heart rate varies continually but this depends on an intact parasympathetic nerve supply. The variation is abolished with atropine but uninfluenced by propranolol and is more pronounced at slow heart rates, during deep breathing, and in younger patients.[3] Diabetics with autonomic neuropathy may have a noticeable reduction in, and sometimes complete absence of, heart-rate variation.

Heart-rate variation can be studied during quiet breathing, deep breathing, or after a single deep inspiration. Deep breathing at six breaths a minute is the most convenient and reproducible technique.[5] The patient sits quietly and breathes deeply at six breaths a minute (five seconds in and five seconds out) for one minute. An electrocardiogram is recorded throughout the period of deep breathing, with a marker used to indicate the onset of each inspiration and expiration.

TABLE I—*Flow plan for performing tests of cardiovascular autonomic function*

Test (in following order)	Position	Approximate time of test (min)	Apparatus required
Heart-rate response to Valsalva manoeuvre	Sitting	5	Aneroid manometer, electrocardiograph
Heart-rate variation during deep breathing	Sitting	2	Electrocardiograph
Blood-pressure response to sustained handgrip	Sitting	5	Handgrip dynamometer, sphygmomanometer
Immediate heart-rate response to standing	Lying to standing	3	Electrocardiograph
Blood-pressure response to standing			Sphygmomanometer

TABLE II—*Normal, borderline, and abnormal values in tests of cardiovascular autonomic function*

	Normal	Borderline	Abnormal
Tests reflecting parasympathetic function			
Heart-rate response to Valsalva manoeuvre (Valsalva ratio)	$\geqslant$1·21	1·11–1·20	$\leqslant$1·10
Heart-rate (R-R interval) variation during deep breathing (maximum-minimum heart rate)	$\geqslant$15 beats/min	11–14 beats/min	$\leqslant$10 beats/min
Immediate heart-rate response to standing (30:15 ratio)	$\geqslant$1·04	1·01–1·03	$\leqslant$1·00
Tests reflecting sympathetic function			
Blood-pressure response to standing (fall in systolic blood pressure)	$\leqslant$10 mm Hg	11–29 mm Hg	$\geqslant$30 mm Hg
Blood-pressure response to sustained handgrip (increase in diastolic blood pressure)	$\geqslant$16 mm Hg	11–15 mm Hg	$\leqslant$10 mm Hg

The maximum and minimum R-R intervals during each breathing cycle are measured with a ruler and converted to beats a minute. The result is then expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats a minute. The test has the advantage of being objective, simple to perform, and requires very little co-operation from the patient. Heart-rate variation has also been measured as the ratio of the heart rate at expiration to that at inspiration, the so-called E:I ratio, but this does not appear to have any advantages.[5]

Immediate heart-rate response to standing

During the change from lying to standing a characteristic immediate rapid increase in heart rate occurs which is maximal at about the 15th beat after standing. A relative overshoot bradycardia then occurs, maximal at about the 30th beat.[6] This response is mediated by the vagus nerve.[7] Diabetics with autonomic neuropathy show only a gradual or no increase in heart rate after standing.

The test is performed with the patient lying quietly on a couch while the heart rate is recorded continuously on an electrocardiograph. The patient is then asked to stand up unaided, and the point at starting to stand is marked on the electrocardiogram.

The shortest R-R interval at or around the 15th beat and the longest R-R interval at around the 30th beat after starting to stand are measured with a ruler. The characteristic heart-rate response is expressed by the 30:15 ratio. Other ways of measuring this response are under debate, but we still recommend the 30:15 ratio. This test is simple and objective, requires little patient co-operation, is reproducible, and does not depend on either age or the resting heart rate.

Tests reflecting sympathetic damage

Blood-pressure response to standing

On standing pooling of blood in the legs causes a fall in blood pressure, which is normally rapidly corrected by peripheral vasoconstriction.[3] In patients with autonomic damage the blood pressure falls on standing and remains lower than in the lying position.

The test is performed by measuring the patient's blood pressure with a sphygmomanometer while he is lying down quietly and again when he stands up. The postural fall in blood pressure is taken as the difference between the systolic blood pressure lying and the systolic blood pressure standing. This simple test gives an abnormal result only with severe peripheral sympathetic damage.

Blood-pressure response to sustained handgrip

During sustained handgrip a sharp rise in blood pressure occurs, due to a heart-rate-dependent increase in cardiac output with unchanged peripheral vascular resistance.[3] Should the normal reflex pathways be damaged, as in diabetics with extensive peripheral sympathetic abnormalities, the rise in blood pressure is abnormally small.

The maximum voluntary contraction is first determined using a handgrip dynamometer. Handgrip is then maintained at 30% of that maximum for as long as possible up to five minutes. Blood pressure is measured three times before and at one-minute intervals during handgrip. The result is expressed as the difference between the highest diastolic blood pressure during handgrip exercise and the mean of the three diastolic blood-pressure readings before handgrip began.

The autonomic "battery" of cardiovascular tests

Table I shows how all five tests can be performed simply and quickly. The total time required is about 20 minutes, and the equipment needed includes a sphygmomanometer, an electrocardiograph, an aneroid manometer, a handgrip dynamometer, plus couch and chair. Once the tests have been performed the results can be calculated either by hand, or, if facilities are available, using a microprocessor system to measure the R-R intervals directly from the electrocardiogram record. Table II gives the normal, borderline, and abnormal values which we use for each test. The results can then be categorised, and usually fall into one of four groups: normal; early parasympathetic damage with results of one of the three tests of parasympathetic function abnormal; definite parasympathetic damage with results of at least two of the tests of parasympathetic function abnormal; and combined parasympathetic and sympathetic damage, where in addition to abnormal parasympathetic test results findings in one or both of the sympathetic tests are abnormal. In our experience with over 500 diabetics very few (20; 4%) could not be placed into one of these categories using this battery of tests.

The natural history of autonomic damage in diabetes is becoming clearer, with parasympathetic damage occurring early and sympathetic damage later.[8 9] These simple tests allow clinicians to give some diagnostic precision to the autonomic abnormalities present in diabetics. Lest it be thought that this is only of limited importance, most large series have found that 20% to 40% of all diabetics have some abnormalities of autonomic function.[10–13]

Treatment of symptoms

Postural hypotension is probably the most disabling symptom of autonomic damage. The different treatments proposed include elastic stockings, ephedrine, tyrosine, indomethacin, and beta-blockers. In diabetics the most effective treatment is probably fludrocortisone, 0·1-0·3 mg daily, which is less than the dose usually required for primary orthostatic hypotension. This drug increases blood volume and minimises the fall in blood pressure. Many diabetics have considerable falls in blood pressure without symptoms and do not need treatment. If fluid retention develops, as with congestive cardiac failure or the nephrotic syndrome, postural hypotension can disappear and so make drug treatment unnecessary. Treatment with insulin can sometimes aggravate postural hypotension, and changing the timing of injections may help.

Gastric symptoms—Experimental studies have shown that metoclopramide increases gastric motility and may improve symptoms in some patients who have symptomatic gastric atony and gastric retention.[14] A dose of 10 mg three times daily before meals is usually adequate.

Diarrhoea—The mechanism of diarrhoea in diabetic autonomic neuropathy is obscure. Broad-spectrum chemotherapy such as tetracycline, given for the episodes or on an intermittent (one week in four) basis, often relieves symptoms, but improvement may coincide with natural remission. Recently metoclopramide given for gastric problems has been noted to lessen diarrhoea in some patients. This seems an effective way of treating diabetic diarrhoea, sometimes with dramatic results, and we now recommend it in a dose of 10 mg three times daily. Only if this is not effective should chemotherapy be given.

Sweating—Troublesome excess sweating can be helped with anticholinergic drugs such as propantheline hydrobromide or poldine methylsulphate, though these drugs do have side effects such as urinary retention. Some diabetics with gustatory sweating find that a prophylactic dose of either drug taken before a heavy meal is effective.

Bladder dysfunction and urinary retention—Patients with autonomic dysfunction of the bladder should be encouraged to void every three to four hours during the day, if necessary using manual suprapubic pressure. Long-term chemotherapy is sometimes required for urinary infection. If the residual urine volume is increased the patient is best treated by bladder-neck resection, provided that he is fit for operation, so allowing the weak bladder muscles to overcome outflow resistance at the bladder neck.

Impotence—Once impotence has developed in diabetics with autonomic neuropathy it is usually irreversible, and counselling probably is the most helpful course of action. Penile prostheses have been developed in the United States but European experience of these is limited.

Cardiorespiratory arrests—Sudden and unexpected deaths occur in diabetics with autonomic neuropathy, and these may be due to cardiorespiratory arrest in association with hypoxia.[2 15] Any diabetic who has autonomic neuropathy is a considerable anaesthetic risk, and particular care needs to be taken during and after the operation to try to prevent suchepisodes, which may be due to sudden changes of the inspired oxygen concentration.

Prevention or reversal of autonomic damage

By the time symptoms have developed autonomic nerve damage is probably irreversible and carries a poor prognosis.[2] As some autonomic damage occurs in many diabetics, however, prevention of the late stages is clearly desirable. Preliminary studies suggest that very good metabolic control can achieve some reversal of autonomic abnormalities. Diabetics with abnormalities of autonomic function should therefore be encouraged to keep their diabetes as well maintained as possible. A second approach to prevention of autonomic damage has been with certain drugs, such as those of the aldose reductase inhibitor group, but as yet it is too early to say whether or not prevention or reversal of the damage is possible by this means.

Conclusions

Subclinical autonomic nerve damage occurs more widely in diabetics than was hitherto suspected and is assuming greater importance because of the implications for morbidity and mortality. Symptomatic autonomic neuropathy carries a worse prognosis than any other complication of diabetes.[2] The simple bedside tests described above can provide an objective guide to whether or not autonomic damage is present, and to what degree. Some of the troublesome symptoms in the later stages can now be more successfully treated than before. The longer-term aim of management should, however, be the prevention or reversal of autonomic damage, particularly in its early stages.

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